Chapter 2

Mitochondria and Heart Disease

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Abstract

Mitochondria play a key role in the normal functioning of the heart and in the pathogenesis and development of various types of heart disease. In addition, specific mitochondrial cardiomyopathies due to mutations in mitochondrial DNA have been identified. Increasing studies demonstrate that mitochondrial function has emerged as a therapeutic target in heart disease. This chapter addresses the recent studies of the role and the mechanism of mitochondria in the development of heart disease, and the progress in clinical diagnosis and treatments on a mitochondrial basis. Consequently, the aim of this chapter is to outline current knowledge about mitochondria in the heart disease.

Keywords: mitochondria, heart, heart failure, cardiac hypertrophy, heart disease

1. Introduction

The heart is the most metabolically active organ in the body and highly depends on oxidative energy generation in mitochondria to supply the large amount of adenosine triphosphate (ATP) required for its continuous contractile activity. In addition, cardiac mitochondria also serve other cellular functions such as generating and regulating reactive oxygen species (ROS), buffering cytosolic calcium ions (Ca^{2+}), and regulating cellular apoptosis through the mitochondrial permeability transition pore (mPTP).

Heart disease is the leading cause of mortality worldwide. Although the study of mitochondrial function in the human heart faces many obstacles, the role of mitochondria in cardiac diseases has been elucidated from the studies with animal models. Increasing evidences have shown that abnormalities in the mitochondrial structure and function are tightly associated with development of various cardiovascular diseases, which prompted new therapies to treat and prevent heart disease by aiming at metabolic modulation.

Mitochondrial abnormalities include impaired mitochondrial electron transport chain (ETC) activity, increased formation of ROS, shifted metabolic substrate utilization, aberrant mitochondrial dynamics, and altered ion homeostasis. Some of the mitochondrial abnormalities may have a genetic basis due to the changes of mitochondrial DNA (mtDNA) or the mutation of specific nuclear DNA (nDNA), while other abnormalities are due to environmental cardiotoxic insult or uncharacterized reasons. Although many specific mitochondrial targets have proven to be promising therapeutic strategies in experimental studies, most of them are pending for validation through clinical trials. Better understanding the molecular mechanism of mitochondria in cardiac pathology is important to provide diagnosis and treatment of mitochondrial-based cardiac diseases.

In order to better understand the role that the mitochondrion plays in the heart, we provide in this chapter a brief background describing the regulation and function of mitochondria during normal cardiac development and aging as well as the pathological mechanisms involved in cardiac diseases. We also address the mitochondrial abnormalities–based diagnosis and therapeutic options available in heart disease.

2. The role of mitochondria in the normal heart

Mitochondria have long been described as the powerhouses of the cell. They are responsible for the generation of ATP, the main energy currency of the cell, while playing important roles in intracellular signaling, activation of apoptosis, and other mechanisms. Little information is currently available on mitochondrial function in the normal human heart as most of the studies on the role of mitochondria have relied on animal models, which may not be representative of the human. However, the development of new methods to study mitochondrial function provides an opportunity to use the small amount of tissue available from surgeries to understand mitochondrial function. In the near future, we expect more studies to be developed utilizing these techniques.

2.1. Basis of the regulation of cardiac mitochondrial function

2.1.1. Cardiac energy production and metabolism

The heart relies mainly on mitochondrial metabolism to provide most of its energy. The heart has the largest demand for energy among all organs, since it beats continuously from its formation in the fetus until death, and thus cardiomyocytes contain the highest concentration of mitochondria in the body in order to meet its energy requirements [1]. Several interacting bioenergetic pathways contribute to energy metabolism of cardiac muscle including pyruvate oxidation, the tricarboxylic acid (TCA) cycle, the mitochondrial fatty acids oxidation (FAO), and oxidative phosphorylation (OXPHOS), which generates 80–90% of cellular ATP [2]. While the oxidation of pyruvate takes place in the cytosol, the other procedures occur in the mitochondria.

In the normal heart tissue, the supply of ATP from glycolytic mechanism is limited [2]. Fatty acids are the primary energy substrates used to produce ATP in cardiac muscle by OXPHOS, utilizing the carnitine shuttle to transport the fatty acids into the mitochondria. The heart also maintains stored high-energy phosphates, such as creatine phosphate (CP), that are produced

from creatine by mitochondrial creatine kinase (mitoCK) using ATP from the closely associated adenine nucleotide translocase (ANT) and mitochondrial ATP synthase [2].

Additionally, the heart is a well vascularized organ, allowing for delivery of freshly oxygenated blood and quick removal of the waste products of metabolism. This constant supply of oxygen is important for OXPHOS to take place, as oxygen serves as the final electron acceptor in the ETC. Understanding the factors involved in the development and function of mitochondrial energy production pathways is increasingly important due to the many diseases associated with defects in this machinery.

Energy production within the cardiomyocytes of the heart is influenced by genetic factors as well as environmental factors. nDNA and mtDNA affect the enzymes and their cofactors as well as the availability of substrates to the mitochondria from their surroundings, which further influence OXPHOS. Cardiac tissue has specific gene regulations to meet its physiological and developmental needs. For example, the ATP synthase β-subunit is expressed at higher levels in cardiomyocyte-differentiated cells compared to control cells [3], and some isoforms of enzymes, e.g., cardiac specific isoforms of cytochrome c oxidase subunits VIa, VIIa, and VIII, are differentially expressed across tissues [4].

Besides the expression and function of the main proteins associated with the OXPHOS, the component of the ETC complexes I-IV and ATP synthase (complex V), many other molecules have been found to be involved in the regulation of the mitochondrial energy production through posttranslational modification. For example, proteins within the mitochondrial complexes can be nitrosylated (the addition of an NO group) or *O*-GlcNAcylated (the addition of *O*-linked β-*N*-acetylglucosamine (*O*-GlcNAc)) [5, 6]. These protein modifications modulate the activity of the complexes and hence change the efficiency of the mitochondria to meet the physiological function of the heart. In addition, our recent studies have also found a specific cell survival-promoting signaling that plays an important regulatory role in promoting ETC efficiency in cardiomyocytes, remarkably under the cardiac stress [7–9]. In particular, we found that this signaling pathway, which includes the heat shock protein 22(Hsp22), AKT, and valosin-containing protein (VCP), promotes ETC efficiency in cardiomyocyte through the increase of mitochondrial inducible nitric oxide synthase (iNOS) [7–9].

2.1.2. Modulation of calcium signaling

Ca^{2+} concentration is highly regulated in the myocardium and is responsible for the induction and intensity of contraction in the myocytes [10]. Mitochondria are able to modulate the Ca^{2+} concentration in the cardiomyocyte, which plays an important role in the cardiac function [11].

Mitochondria can directly decrease the Ca^{2+} concentration in the cytosol of the cell by importing Ca^{2+} via the mitochondrial Ca^{2+} uniporter. Reciprocally, they can also increase the Ca^{2+} concentration in the cytosol by expelling calcium stored within the mitochondria through Na^{+}/Ca^{2+} or H^{+}/Ca^{2+} exchangers [12]. This elaborate system of channels and transporters allows for physiological responses to cytosolic calcium signals and the loading of Ca^{2+} in the mitochondrial matrix. Mitochondria partake in the cardiac excitation-contraction coupling (ECC) by storing Ca^{2+}, responding to cytosolic calcium signals and generating the ATP required for cardiac contraction. Ca^{2+} influx via L-type Ca^{2+} channels triggers further release of Ca^{2+} from

the sarcoplasmic reticulum (SR), which binds to troponin C, and allows for the myosin and actin filaments to interact [10]. During diastole, the Ca^{2+} either goes back into the SR or is exported out of the cell via the Na^{+}/Ca^{2+} exchanger [13]. An increase in workload, as triggered by β-adrenergic stimulation, increases the number of Ca^{2+} transients as well as the size of the transients, leading to stronger cardiac contractions [14]. Additionally, mitochondria can also indirectly contribute to Ca^{2+} regulation by inducing changes in the concentration of ATP, NAD(P)H, pyruvate, and ROS, which in turn regulate other Ca^{2+} signaling machinery components [15]. This associated Ca^{2+} signaling is involved in the Ca^{2+} buffering, the Ca^{2+} release from internal stores and the influx from the extracellular solution, the Ca^{2+} uptake into cellular organelles, and the extrusion by plasma membrane Ca^{2+} pumps [16].

Calcium signaling in the mitochondria also contributes to the regulation of cellular energy metabolism. ATP is hydrolyzed to ADP in order to power energy-requiring processes and is shuttled into the mitochondria to be reconverted into ATP as a final step in respiration. This enhances the electron flux within the ETC, resulting in the oxidation of NADH to NAD^{+}. Concurrently, Ca^{2+} is transferred into the mitochondria through the mitochondrial Ca^{2+} uniporter (MCU), activating the enzymes of the Krebs cycle to adjust NADH regeneration to match its oxidation [14]. In addition, excessive mitochondrial Ca^{2+} uptake and Ca^{2+} accumulation, irreversible $\Delta\Psi$ collapse, ATP depletion, and oxidative stress contribute to the opening of the mPTP [17].

Type 2 ryanodine receptors (RyR2s) and type 2 inositol 1,4,5-trisphosphate receptors (IP3R2s) are Ca^{2+} release channels found on cardiac SR. Recent studies have demonstrated that leaky RyR2 channels, but not IP3R2, contribute to mitochondrial Ca^{2+} overload and dysfunction in heart failure (HF) [11]. NO signaling and its downstream effectors such as *S*-nitrosylation have also been shown to be key processes in regulating calcium signaling. The neuronal nitric oxide synthase (nNOS or NOS1) has been linked to the reduction of calcium influx through the L-type Ca^{2+} channel [5, 18]. This decrease in Ca^{2+} influx may be responsible for the cardioprotection induced by NO. Furthermore, decreased *S*-nitrosylation of key SR Ca^{2+} handling proteins such as the RyR2s due to impaired NOS1 can result in increased Ca^{2+}-mediated ventricular arrhythmia in the setting of elevated myocardia $[Ca^{2+}]_i$ [19]. Inhibition of *S*-nitrosylation of the SR Ca^{2+} ATPase (SERCA) has been associated with lower Ca^{2+} uptake in the SR and impaired myocardial relaxation [20].

While substantial efforts were undertaken to characterize the kinetic properties of mitochondrial calcium cycling, the experimental approaches and techniques have not been able to reach explicit conclusions on cardiac mitochondrial responses to cytosolic Ca^{2+} oscillations during each heartbeat. However, it is widely accepted that Ca^{2+} is a second messenger for the regulation of mitochondrial tasks and represents a crucial link for the role of mitochondria for excitation-metabolism and excitation-contraction coupling in the heart.

2.1.3. Generation of ROS

Mitochondria are also a large cellular source of ROS. ROS includes the superoxide anion radical ($O_2^{\cdot-}$) and hydroxyl radical ($^{\cdot}OH$), as well as nonradical oxidants, such as hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$) [21]. They can be converted from one to the other by enzymatic and nonenzymatic mechanisms. The most abundant form of ROS in the body is $O_2^{\cdot-}$, which is enzymatically or spontaneously dismutated to H_2O_2. In the human body, there are

three superoxide dismutase (SOD) isoforms with precise subcellular compartmentalization: the Cu,Zn-dependent isoform (Cu,Zn SOD, SOD1) is found in the cytosol; the Mn-dependent isoform (Mn SOD, SOD2) is located in the mitochondrial matrix; and Cu,Zn SOD is located in the extracellular space (ecSOD, SOD3) [22]. Mitochondrial ROS have emerged as an important mechanism of disease and redox signaling in the cardiovascular system.

$O_2^{\cdot-}$ is the proximal mitochondrial ROS and is produced by the one-electron reduction of oxygen [23]. Mitochondrial $O_2^{\cdot-}$ production takes place at redox-active prosthetic groups within proteins where the kinetic factors are key to the production of $O_2^{\cdot-}$ formation [23]. Under physiological conditions, the balance between ROS generation and ROS scavenging is highly controlled. ROS generation can initiate diverse cellular responses, which include triggering signaling pathways involved in cell protection, initiating coordinated activation of mitochondrial fission and autophagy to optimize removal of abnormal mitochondria and cells, and ensuring that the damage does not spread to neighboring mitochondria and cells [21]. Both high levels of ROS (oxidative stress) and excessively low levels of ROS (reductive stress) are harmful and may play causative roles in the pathologies related to the dramatic change of redox environment [21]. Excess ROS production in the heart under pathophysiological conditions leads to mitochondrial dysfunction and bioenergetic decline and contributes to a number of cell pathologies in the heart. For example, ROS is favored by high membrane potential, low ATP formation, and hampering the flow of electrons through the complexes in cardiomyocytes. In addition, ROS formation is the result of the uncoupling of respiration as seen during the opening of the mPTP [21]. Although many studies have detected $O_2^{\cdot-}$ produced in isolated mitochondria, there are few reliable methods that can be used to measure the mitochondrial ROS production *in vivo* [24].

The molecular mechanisms of ROS generation in the cardiac mitochondrion remain unclear. It has been showed that complex I (NADH-ubiquinone oxidoreductase) is the main source of ROS in the mitochondrion. However, the ROS production at complex I is high under pathological conditions, not physiological condition [21]. Further mechanistic studies suggest that the major site of ROS production in complex I is either upstream of a rotenone-binding site or tightly coupled to the increased level of NAD(P)H after rotenone supplementation [21]. ROS production at complex II is low at physiological concentrations of succinate, suggesting that complex II is not a key contributor to the mitochondrial ROS. ROS production at complex III only occurs after the binding of antimycin A, suggesting that conformational changes that occur on antimycin A binding may be responsible for the production of ROS [21].

2.1.4. mPTP opening

Mitochondria can mediate cell death through the opening or activation of the mPTP [25]. The mPTP is a high conductance channel that generates a sudden increase in inner mitochondrial membrane (IMM) permeability to ions and small solutes when opened [26, 27]. The pore is regulated by the concentration of Ca^{2+}, ADP, NADH, and ROS. Regulation of the mPTP opening is a key essential mechanism for cardiomyocyte survival and function.

Intense research efforts have been focused on elucidating the molecular components of the mPTP. The original mPTP model hypothesized that the channel comprised these principal proteins: cyclophilin D (CyPD), located in the mitochondrial matrix; the ANT, found in the inner membrane; the voltage-dependent anion channel (VDAC) in the outer membrane [28];

and other interacting mitochondrial molecules such as the phosphate carrier, BH3 proteins, and p53 [29]. However, genetic ablation of the proposed components revealed that only the deletion of the CyPD gene resulted in impaired opening of the mPTP, suggesting that the other proposed components are not a necessary part of the pore [30, 31].

Recent studies indicated that the ATP synthase is a major component of the mPTP [32]. There are two working proposals about the mechanism for ATP synthase in the mPTP formation. The first one suggests that the pore forms at the interface of two dimers of ATP synthase [33]. It has been showed that the current that was observed from reconstituted lipid bilayers with purified dimers of the ATP synthase was electrophysiologically equivalent to that of the mPTP. Additionally, genetic ablation of two specific subunits of the F0 subcomplex that are necessary for dimerization did not result in opening of the pore, which further underscores the importance of dimerization for the formation of the mPTP [34]. The second hypothesis focuses on the c-subunit ring of the F0 subcomplex [35]. In purified ATP synthase extracts in yeast, the ring structure produced by the c-subunits exhibited a current that was equivalent to that of the mPTP [34], and the currents were inhibited by regulators of the mPTP, suggesting that the ring and the mPTP are the same. While debate continues about the precise components and mechanism of the mPTP, its importance in physiology and pathology is clear and its regulation is paramount to cell survival.

While a short-term opening of the mPTP appears to act as a normal calcium-release mechanism that is required for proper metabolic regulation [29, 36–38], irreversible formation and consequent opening of the mPTP are key factors in mitochondrial dysfunction and mitochondria-driven cell death [32, 39, 40]. When the mitochondria are exposed to high concentrations of calcium, they undergo a massive and permanent swelling that leads to an abrupt increase in permeability to small solutes of the IMM, abolishing the chemiosmotic gradient across the IMM [29], which subsequently uncouples OXPHOS, leading to a decrease in ATP production and an increase in ROS formation [25]. Further rupture of the outer mitochondrial membrane results in the extrusion of cytochrome c, a key step in the initiation of apoptosis [41]. The mPTP may also play a role in the regulation of energy production due to the dual role of the ATP synthase in both ATP production and mPTP formation [25].

Interestingly, small increases in *O*-GlcNAcylation were correlated with improved ability of cardiac mitochondria to sequester Ca^{2+} as well as resistance to mPTP opening. Key regulatory proteins in the mPTP, the VDAC and ANT, were also found to be able to be *O*-GlcNAcylated. The ATP synthase, the key molecule that forms the mPTP, has also been shown to be able to be *O*-GlcNAcylated [6]. Since mPTP opening is influenced by the loss of the mitochondrial potential as well as calcium overload, any change in mitochondrial potential or calcium dynamics may have adverse effects in the mitochondria. Key calcium signaling participants of mPTP regulation include the pore of the outer membrane, VDAC, the pore of the IMM calcium uniporter, and a key regulator of the mPTP, cyclophilin D [42]. Our most recent study also showed that overexpression of VCP protects against stress-induced mPTP opening in cardiomyocyte through an iNOS-dependent mechanism [9].

2.2. Cardiac mitochondrial changes during cardiac development

There are significant differences in mitochondrial metabolism and function during the cardiac development through the fetus, neonatal, and adult heart.

One of the major changes during the cardiac development is the use of energy fuels to generate ATP in cardiomyocyte. In the fetal heart, glucose and lactate are the predominant substrates used in the generation of ATP [43, 44]. The fetal heart boasts of a large endogenous glycogen supply, which is a significant source of the glucose on which the heart relies. Glycogenolysis is also particularly important in conditions of oxygen deprivation, allowing the fetal heart to resist the effects of hypoxia and ischemia better than the adult heart [43]. Fetal hearts have less mitochondria and therefore lower levels of respiratory and TCA cycle activities [2]. Notably, circulating levels of fatty acids are low, reducing the role of FAO in the generation of ATP. FAO is further inhibited by the high lactate levels present in the fetal heart [2]. Postnatally, an important switch occurs as fatty acids replace glucose and lactate as the primary energy substrates in the developing heart [43]. Consequently, the activity of the proteins of the carnitine shuttle, particularly the M isoform of the mitochondrial carnitine palmitoyltransferase I (CPT I) and mitochondrial carnitine palmitoyltransferase II (CPT II), is markedly increased during the early postnatal period [45]. Other key proteins that have been associated with the uptake of fatty acids into cardiac muscle cells also exhibit increased mRNA expression during maturation of the heart, reflecting increased fatty acid uptake and metabolism [46].

In addition, there is a change in the transfer and use of the energy currency in the mitochondria during the cardiac development. MitoCK is responsible for the production of high-energy phosphates in adult heart. In the fetal heart, mitoCK levels are undetectable, with its expression starting between weeks 1 and 2 in the Wistar rat pup and rising to adult levels after 6 weeks [47]. MitoCK expression was associated with creatine-activated respiration and the affinity of OXPHOS to ADP. Importantly, there is a change in the organization of the cardiac mitochondria from a random arrangement from day 1 in a rat to a fine network of myofibrils by week 3, as mitoCK allows maximal activation of the processes of OXPHOS [47].

2.3. Cardiac mitochondria during aging

Aging is a major risk factor for cardiovascular diseases. During aging, mitochondrial oxidative stress responses, mitochondrial damage, and biogenesis as well as the cross-talk between mitochondria and cellular signaling are changed.

Aging may induce changes to the shape and size of mitochondria in the heart [48]. In aged mice, mitochondria appeared more rounded and less spherical [49]. It was further noted that aged mitochondria exhibit a lower total area of inner membrane per mitochondria, suggesting a reduced capacity for OXPHOS [50]. Reciprocally, increased levels of large-scale deletions and point mutations in cardiac mtDNA, as well as reduced levels of mitochondrial enzymatic activities, may occur with aging.

Additionally, the multiple metabolic changes that occur in cardiac muscle with advancing age include increasing levels of saturated fatty acids and reduced levels of polyunsaturated fatty acids and cardiolipin [51]. Cardiolipin is a key cellular phospholipid and an important constituent of the mitochondrial inner membrane. Reduced cardiolipin influences cardiac mitochondrial membrane transport function, fluidity, and stability of the membrane and facilitates optimal energy generation [51]. Significant reduction in carnitine and acetyl carnitine levels has also been reported in older subjects, suggesting lowered ability to transfer fatty acids into the mitochondria to be metabolized [52]. In addition, the effect of aging on cardiac OXPHOS

enzymatic function has been reported. Within cardiomyocytes, the interfibrillar mitochondria consume less oxygen and show a decrease in the ETC enzyme activity, particularly complexes III and IV during aging [53, 54]. This decrease in enzyme activity may lead to the lowered ability to meet the energy demands of the heart as aging ensues.

Furthermore, mitochondrial abnormalities have been proposed due to the increased mitochondrial production of ROS during aging. The rate of oxidative phosphorylation decreases with aging, allowing for increased leakage of electrons [48], these electrons are then able to interact with oxygen, generating superoxide anions and other forms of ROS. Excessive ROS formation has harmful consequences, including cellular dysfunction and cell death [48]. This high level of ROS is also able to oxidize mtDNA. Moreover, opening of the mPTP has been found to be changed in the heart during aging [55]. Increased opening of the mPTP may be linked to higher ROS levels and thus may be facilitating the aging process.

3. Mitochondria in heart diseases

Although the pathophysiology of heart diseases is divergent, mitochondrial dysfunction appears to be a common mechanism that determines cardiac survival and function. Cardiac mitochondrial abnormalities include shifted metabolic substrate utilization, impaired mitochondrial ETC activity, increased formation of ROS, altered calcium homeostasis, and increased mPTP opening. Defects in mitochondrial structure and function have been found in association with cardiovascular diseases such as dilated and hypertrophic cardiomyopathy (DCM and HCM, respectively), cardiac conduction defects and sudden death, ischemic and alcoholic cardiomyopathy, and myocarditis. This section focuses on the changes of mitochondrial bioenergetics that are associated with cardiac survival and growth in heart diseases, including heart failure (HF), ischemia/reperfusion (I/R), pressure overload–induced cardiac hypertrophy and the cardiomyopathies in diabetes, and genetic mitochondrial diseases (MD).

3.1. Mitochondrial dysfunction in HF

HF is an end stage of many heart disorders and a complex chronic clinical syndrome. Although the causes of HF are variable, HF is viewed as an energy-mismatched disease [1, 56]. The first link between HF and mitochondrial dysfunction was described in 1962 in a guinea pig model with HF induced by an aortic restriction [57]. Since this observation, there has been growing interest in the investigation of mitochondrial function in failing hearts [58], and emerging evidence supports the concept that dysregulation of myocardial energetics is tightly associated with the development and progression of HF [1, 56, 59, 60].

The heart requires large amounts of energy to facilitate its continuous contraction and relaxation cycles. HF occurs when the energy demand outweighs the energy supply. Any contributor that leads to HF is accompanied with a gradual but progressive decline in the activity of mitochondrial respiration, leading to diminished capacity for ATP production and subsequent progression of the heart to fail. Reciprocally, a failed heart reduces the blood and oxygen supply to the peripheral tissues and to the heart itself, further exacerbating the decline in cardiac energy production. On the other hand, the amount of ATP required from the mitochondria is increased to meet the abnormally enlarged myocardium size and failing function, augmenting

the imbalance between the requirement and supplement of oxygen in the cardiac muscle during the contraction and relaxation cycle. Consequently, the bioenergetic requirements of the heart are beyond what the mitochondria can cope with, and the heart begins to progress to HF. Thus, energy deficiency can be a cause and effect of HF. There are considerable evidences of links between HF and impairment of the energetics of myocardial mitochondria, such as declined mitochondrial synthesis/resynthesis of ATP, shifted fuel selection, impaired mitochondrial biogenesis, and abnormal calcium transport.

3.1.1. Reduction of ATP synthesis

Like all the other cells, there are three energy systems that contribute to the production of ATP in cardiac muscles: phosphagen system (ATP-creatine phosphate cycling; high power, short duration), glycolysis (moderate power/short duration), and FAO (low power/long duration). Three energy systems can be selectively recruited, depending on the amount of oxygen available, as part of the cellular respiration process to generate the ATP for the cardiac muscles. Since the heart has a limited capacity for substrate storage, energy is required to rebuild or resynthesize it. The energy released from any of these three series of reactions is coupled with the energy requirements of the reaction that resynthesizes ATP.

ATP-CP system is the quickest way to resynthesize ATP. CP, like ATP, is stored in cardiac muscle cells and serves as the main energy store in myocardium. If oxygen is unavailable, the ATP-CP system does not use oxygen and does not produce lactic acid. This is the primary system behind the very short, powerful movements of the cardiac contraction and relaxation cycle. When CP is broken down, a large amount of energy is released. This energy released is coupled to the energy requirement necessary for the resynthesis of ATP. CP can easily diffuse through the inner mitochondrial membrane to the cytosol to generate ATP from ADP catalyzed by the cytosolic CK (cytoCK). Normal beating cardiomyocytes, even under variations of workload, maintain a constant level of ATP and CP in the cytosolic and mitochondrial compartments [58]. The CP/ATP ratio of 1.7–2.1 reflects normal mitochondrial ATP production and CK efficiency. This ratio has become a powerful index of the bioenergetics of the heart and its decrease has been reported in both the human and animal models of HF [61–65]. In HF patients and animal models, the total CK, as well as both the cytoCK and mitoCK, positively correlates with ejection fraction and can decrease as much as 50% [66–68]. It is observed that the decrease in CK activity, rather than the level of hypertrophy itself, is a hallmark of the transition from severe hypertrophy to HF [62, 69]. Interestingly, healthy myocardial cell size, myofibrillar and cytoskeletal organization, and positioning of the mitochondria near the SR allow for the ATP production in both mitochondrial and cytosolic regions and work concurrently to meet the energy demand [69]. However, in the failing hearts, the increase in myocardial cell size, the shrinkage of mitochondrial content, the alterations in microtubules, and the disorganization of cytoskeletal protein and their reduced expression contribute to decrease the efficiency of mitoCK and cytoCK for the energy transfer between the mitochondria and the cytosol [70–73].

The glycolysis system is the second-fastest way to resynthesize ATP. In the normal heart, pyruvate is converted into a metabolic intermediary molecule called acetyl coenzyme A (acetyl-CoA), which enters the mitochondria for oxidation and the production of more ATP. In the failing heart, the conversion to lactate occurs due to the greater demand for oxygen than the available supply. Although the catabolism of sugar supplies the necessary energy from which

ATP is manufactured, it is only partially broken down when sugar is metabolized anaerobically. Only a few moles of ATP can be resynthesized from the breakdown of sugar as compared to the yield possible when oxygen is present. In addition, there is an increase in hydrogen ions due to the formation of lactic acid, causing the muscle pH to decrease. This leads to acidosis and the accumulation of other metabolites such as ADP, P_i, and potassium ions that may further induce the inhibition of specific enzymes involved in metabolism and muscle contraction.

The aerobic system includes the Krebs cycle and the ETC. Mitochondria are crucial for the working of the cardiomyocytes as these powerhouses provide the aerobic metabolism for the cardiomyocyte function. Reduced mitochondrial oxidative capacity has been observed in rodent HF models. The onset of HF is not an overnight process but a progression of continual abnormalities in the bioenergetics due to the disruption of metabolic regulatory signaling pathway or the lack of oxygen supply, which leads to failure in mitochondrial dysfunction and decline in ATP production.

3.1.2. The shift of fuel selection of mitochondrial bioenergetics

Numerous studies have demonstrated that cardiac substrate preference is altered in the failing heart. Fatty acids are the preferential energy substrates of the heart and contribute to 60–90% of cardiac ATP production [74]. At the early phase of HF, there is a decline in FAO. An adaptive mechanism is to switch from fatty acid to glucose via the glycolytic pathway. The decrease in the capacity for the mitochondria to oxidize fatty acids is linked to the reduced expression of the master regulator of energy metabolism in mitochondria, PGC-1α (transcriptional co-activator peroxisome proliferator–activated receptor-γ coactivator-1α) [75–77]. In mouse model, PGC-1α is shown to be crucial for the functional efficiency of mitochondrial FAO, lipid regulation, and ATP synthesis, particularly in instances of increased cardiac demand [78]. The overexpression of PGC-1α in transgenic mice induces enhancement of mitochondrial respiration and an increase in mitochondrial numbers [79]. The downregulation of PGC-1α leads to reduction of its downstream targets, e.g., nuclear respiratory factor (NRFs), estrogen receptor–related receptor (ERRα/γ), peroxisome proliferator–activated receptors (PPARs), and subsequently regulates FAO, glucose utilization, and mitochondrial biogenesis [1, 69]. PPARα, as a transcription factor that enables fatty acids to be transported into the mitochondria and peroxisomes, is downregulated in failing hearts of animals and humans [80, 81]. In human HF patients (both ischemic and idiopathic DCM), ERRα and its target genes were downregulated, which may contribute to the reduction of mitochondrial metabolic capacity [81].

It is yet unclear whether the myocardial substrate shifts serve as adaptive functions or cause deleterious effects on the failing heart, but the evidences from reports in animal models and in rare genetic human diseases provide some light. In mice studies, the rapid decline in the cardiac mitochondrial FAO capacity induces cardio-lipotoxic effects due to the accumulation of lipids [82, 83]. Furthermore, when FAO enzymes such as the very-long-chain acyl-CoA dehydrogenase (VLCAD) or the long-chain acyl-CoA dehydrogenase (LCAD) are disrupted in mice, cardiomyopathic profiles similar to human cases are observed [84, 85]. Likewise, with cardiac-specific deletion of the PPARβ gene, which is involved in the oxidation of the FA, the mice developed cardiomyopathy with cardiomyocyte apoptosis and death [86]. Moreover, in human cases, reports of deficiencies in children of enzymes that are part of the mitochondrial long-chain FAO have caused a stress-induced cardiomyopathy due to accumulation of myocardial lipids [87]. Despite

these evidences of the cardiac pathologies that come from reduced mitochondrial FAO, the shift from FAO to glucose in the hypertrophied heart may be beneficial and adaptive for the short term. PPARα-null mice, for example, have reduced FAO efficiency, but the hearts showed no ventricular dysfunction. However, in a rat pressure overload model, when FAO was reactivated, the hearts developed ventricular dysfunction [88]. In addition, the degree and duration of the pathophysiological stimulus as well as the systemic metabolic state (e.g., levels of circulating lipids) may contribute to the consequence of alterations of FAO capacity in the pathogenesis of HF.

3.1.3. Dysregulation of Ca^{2+} homeostasis

The reduction of energy production rate in dysfunctional mitochondria is also attributed by the dysregulation of Ca^{2+} homeostasis within the cardiomyocyte. Mitochondria act as a calcium sensor detecting the increase and decrease of the cytosolic Ca^{2+} to meet the needs of the cardiomyocyte. Ca^{2+} is transported into the mitochondria via MCU and out of the mitochondria via the sodium-calcium exchanger (NCX). Both the MCU and mitochondrial NCX are localized to the IMM. In normal physiological conditions, in the event of increased workload, the cytosolic Ca^{2+} is increased, triggering the opening of the MCU to transport Ca^{2+} into the mitochondrial matrix. The influx of the mitochondrial Ca^{2+} in the matrix increases the ATP synthase and the dehydrogenase activity of the citric acid cycle to generate more ATP [58]. Another transporter of Ca^{2+} into the mitochondria is the mPTP, which requires oxidative stress, elevated phosphate, and adenine nucleotide depletion to be opened. Increased uptake of Ca^{2+} into the mitochondria has been linked to cellular dysfunction and energy reduction [89, 90]. Also, the accumulation of Ca^{2+} in the mitochondria induces activation of the apoptotic and necrotic pathways [91]. In addition, in postmyocardial infarction HF mouse model, diastolic SR Ca^{2+} leak induces mitochondrial Ca^{2+} overload and dysfunction [92]. In HF, Ca/calmodulin-dependent protein kinase II (CamKII) has been involved in increasing mitochondrial Ca^{2+} uptake through the MCU and promotes mPTP opening and myocardial cell death [93].

3.1.4. Impaired mitochondrial biogenesis

Efficient mitochondrial capacity to meet the heart's workload also involves maintaining and protecting its biogenesis. It has been shown that the mitochondrial biogenesis was declined in failing heart, which is associated with the downregulation of the transcription factors such as NRF and ERRα [94].

3.1.5. Excess generation of ROS

The respiratory chain regularly generates ROS in the form of $O_2^{\cdot-}$, which can initiate the formation of other ROS such as OH, peroxynitrite, and H_2O_2. These $O_2^{\cdot-}$ are not able to easily permeate outside the mitochondria and become trapped within. Since mtDNA has no protective histones and a poor DNA repair system, mtDNA is more susceptible to damage and has a high mutation rate [58]. Presence of ROS generates oxidative stress and damage not only to DNA, but also to proteins of the cell, which include those in signaling of the mechanical and structural roles. In a canine model of HF and HF patient blood samples, $O_2^{\cdot-}$ production by the mitochondria is increased [95, 96]. The reduction of PGC-1α in HF has also been found to promote oxidative stress and mitochondrial damage [97]. Another source of ROS is one of the

isoforms of NADP oxidase (Nox). Nox 4 is abundant in cardiomyocytes and is localized primarily in the mitochondria. Nox 4 has been reported to enhance ROS production in aging and in pressure overload–HF models [98–100] and also is highly active in failing human hearts [101]. Moreover, ROS plays a part in regulating cardiac hypertrophic pathways: Ras, protein kinase C, Jun N-terminal kinase, and mitogen-activated protein kinase [94, 102].

In summary, HF is characterized by bioenergetic imbalance between the energy production from mitochondria and demands from the myocardial performance. There are many complex simultaneous interplays between: the maintenance of ratio of CP/ATP, the level of total CK as a catalyst, the cycling of Ca^{2+} between the cytosol and the mitochondrial matrix, the major regulatory role of PGC-1α for mitochondrial biogenesis, FAO and glucose metabolism, and even the volume of cardiomyocyte in affecting mitochondria positioning that influences efficiency of ATP production in cardiac mitochondria.

3.2. Mitochondria and ischemia/reperfusion (I/R)

The normal function of the mitochondria maintains the endurance of the cardiomyocyte in the events of stress and increased workload. However, as soon as the series of biochemical alterations and damage in the mitochondria occur, the cell viability declines and regresses to cell death. Mitochondrial dysfunction contributes to cell damage during I/R. Myocardial ischemia is the result of the narrowing or blockage of the coronary artery, thereby depriving the cardiomyocytes from oxygen leading to hypoxia and damage to the heart region and disabling the heart to efficiently pump. The effects of hypoxia induce sudden biochemical and metabolic changes in the cardiomyocytes. These alterations induce mitochondrial membrane depolarization, reduction of ATP synthesis, and damage to the contractile function. With the cardiomyocytes being devoid of O_2, the cell metabolism changes to anaerobic respiration, inducing lactate accumulation and pH reduction. The increase in proton drives the Na^+-H^+ ion exchanger to expel H^+ from the cell in exchange for entry of Na^+ ions [103]. Furthermore, due to the lack of ATP, 3Na^+-2 K^+ATPase fail to function causing more accumulation of Na^+ and inducing the reverse function of the NCX pump to extrude Na^+ and accumulate Ca^{2+} ions, promoting Ca^{2+} overload [104]. However, with prolonged ischemia, the increase in mitochondrial Ca^{2+}, ROS, and decline of ATP level, the mPTP is triggered to be opened. These changes further result in mPTP opening, mediating both the necrotic and apoptotic cell death.

Although reperfusion restores the region of ischemia with new influx of O_2, and the necessary substrates for aerobic ATP synthesis are delivered and extracellular pH has been restored, reperfusion has been proven to deliver damage at the same time. As blood flow reintroduces molecular oxygen to the damaged areas, ROS is generated. While the mitochondria generate ROS in normal physiology, the reperfusion of the ischemic region induces bursts of ROS production that overwhelms the ability of the cells to normally scavenge the reactive species [105]. It has been reported that upon reperfusion, while O_2 supply is suddenly restored, the rapid normalization of the pH and the existing Ca^{2+} overload and oxidative stress triggers the mPTP to be opened [106, 107]. If the duration of the ischemia is relatively short, the biochemical changes would not be as severe, mPTP remains closed, and the cell will recover [58]. The activation of mPTP occurs in two stages [107]. In the first stage, during ischemia, due to the accumulation of fatty acids, loss of cytochrome c and antioxidants, the dissipation of the electrical potential across the membrane establishes the ‘priming’ formation of the mPTP. When

reperfusion is introduced, the opening of the mPTP is triggered by multiple factors such as Ca^{2+} overload, increased free phosphate, ROS, and acidosis [107]. In addition, as the mitochondrial membrane potential continues to decline, mitochondrial and cytosolic Ca^{2+} levels continue to increase, leading to cell necrosis and apoptosis.

3.3. Mitochondria and pressure overload–induced cardiac remodeling

Under physiological or pathological cardiac workload, the heart adapts through structural remodeling to meet the requirements. Remodeling at the cellular level induces alterations in organelle structure, intercellular protein, and gene expression [108]. At the early stages of cardiac hypertrophy, there are enhancement and preservation of the mitochondrial oxidative capacity, but as hypertrophy progresses to HF, mitochondrial function is gradually impaired [109]. Mitochondrial alterations and dysfunction have been linked to cardiac remodeling including morphology, FAO, ATP synthesis, biogenesis, ROS, and mitophagy.

It has been widely accepted that pressure overload–induced cardiac remodeling alters the mitochondrial morphology in size, volume, and numbers. For example, the mitochondria were found to be swollen, with degraded mtDNA and altered cristae structures in HCM model in pigs [110]. There were distorted cristae and reduced mitochondrial density and volume in a pressure overload–induced cardiac hypertrophic mouse model without difference in mitochondrial numbers between the hypertrophic hearts and the sham control [111]. Despite these evidence from animal models, observations from electron microscopy show remarkable variabilities in HF patients of cardiomyopathy in terms of the mitochondrial numbers, size, and matrix density [112].

In addition, in the pressure overloaded heart, the fuel that drives mitochondria to synthesize ATP switches from FA to glucose, which causes lesser ATP production and depletion in cellular energy. In normal physiology, the uptake of FAs involves the conjugation of FA to acetyl CoA (FA-CoA). FA-CoA enters the mitochondrial matrix and is metabolized by the beta oxidation process through the carnitine shuttle, CPT-1 and CPT-2 [113]. In the pressure overload heart, FAO rate is reduced, along with the decrease in mRNA expression of CPT-1 [114–116]; however, some report it to be unchanged [113]. The variable data might be due to the varying degrees of hypertrophy in different animals [113].

Furthermore, pressure overload–induced cardiac remodeling also affects mitochondrial biogenesis. In response to metabolic status of the cell, the mitochondria undergo controlled cycles of biogenesis with fusion and fission. The processes of the fusion and fission are well regulated by PGC-1α, which then regulates ERRα to act on the group of guanosine triphosphatases (GTPases). Fusion involves mitofusin proteins (MFN 1 and 2) in the outer mitochondrial membrane and optical atrophy protein 1 (OPA1) in the IMM. The fusion process is switched on to balance the mitochondrial membrane potential and allows for the exchange of matrix components, as well as damaged mtDNA [117]. Fission, on the other hand, allows for more mitochondria to be distributed further to release cytochrome c during apoptosis and mitochondrial degradation by mitophagy. Fission occurs through dynamin-1-like protein (DRP1), mitochondrial fission factor (MFF), and adapter protein mitochondrial fission 1 (FIS1). In physiological hypertrophy, PGC-1α activates biogenesis to meet the demands of the heart [77]. At early stages of pathological hypertrophy, mitochondrial biogenesis increases, and mitochondrial numbers increase, but as hypertrophy worsens to HF, PGC-1α expression is downregulated and biogenesis activity is impaired [79, 118]. In addition, as hypertrophy

transits to HF, the expression of OPA1 is reduced and mitochondria become small and fragmented. Furthermore, in decompensated hypertrophy and HF, the mitochondrial biogenesis also declines due to depletion of ATP synthesis, which then halts the increase in new mitochondria in the cardiomyocyte [109].

Moreover, cardiac hypertrophy also affects the energetic cross-talk between mitochondria and other organelles to transfer ATP. There is direct communication between the mitochondria and the ATPases of the myofibrils and the SR [119]. Muscle mitochondria in its ordered bundled organization around the myofibrils and the SR are highly clustered at regions of high-energy demand where there is a tightly regulated ATP/ADP ratio [69]. In the pressure overload–induced hypertrophic heart, the direct channeling of ATP within the high-energy demand sites becomes weakened due to the decrease in mitochondrial content and numbers [69, 119]. In addition, mitophagy is activated in pressure overloaded cardiomyocytes due to the increased cellular damage from mitochondrial dysfunction. The causative factors of autophagy in cardiac hypertrophy are complex. Although low baseline autophagy allows the cardiomyocytes to adapt to hypertrophic demands, exacerbation of autophagy promotes hypertrophic contractile dysfunction [120].

In summary, pressure overload causes cardiac remodeling through disruption of the cell signaling pathway, altering the mitochondrial morphology in size, volume, and numbers, regulating the mitochondrial biogenesis and affecting the energetic cross-talk between mitochondria and other organelles to transfer ATP for utilization by the cardiomyocyte or mitophagy. These changes further lead to the failing of the myocardium.

3.4. Mitochondria and diabetic cardiomyopathy

Although coronary artery disease remains as the top cause of mortality and morbidity in western countries, the link between HF and diabetes is growing with the rising incidence of diabetes and prediabetes [121]. Based on epidemiological studies, diabetic individuals are likely to develop HF compared to those who have no diabetic history [122]. This link describes the term diabetic cardiomyopathy, which is due to the myocardium of chronic diabetes patients showing diastolic dysfunction and left ventricular hypertrophy, followed by later onset systolic dysfunction that regresses to decompensated HF [123]. Approximately 60% of type 2 diabetic patients have diabetic cardiomyopathy [124]. The causes of diabetic cardiomyopathy are multifactorial and complex. Cardiac mitochondrial abnormalities were found in both diabetic mouse models and human diabetic hearts. Diabetic cardiomyopathy has been linked to the increased myocardial oxygen consumption and increased oxidative stress. Mouse models of type 2 diabetes (*db*/*db* and *ob*/*ob*) showed dysfunctional mitochondrial state 3 respiration and decline in ATP production [125, 126]. In right atrial myofibers of diabetic patients, defects in respiratory complex were observed with the reduction of state 3 respiration on impairment in complex I alone [127]. Another respiration deficiency was detected in myofibers from diabetic patients that showed deficiency in respiration with substrate palmitoyl-L-carnitine [127].

Interestingly, opposite to the reduction of FAO in failing heart, diabetic hearts had more FAO and a reduction in glucose oxidation. The increase in FAO is attributed to the increased expression of PPARα, which increases the genes that are involved with cardiac FA utilization [128]. Additionally, in type 2 diabetes, reduction of cardiac efficiency is also caused by an increase in mitochondrial

uncoupling that in turn increases O_2 consumption. The series of events begins with the increased availability and delivery of FA that forces the mitochondria to increase FA uptake. This stimulates the increase in ROS production [129]. ROS generation activates the uncoupling proteins (UCs) and promotes proton leak via ANT. The increase in mitochondrial uncoupling propagates the increase of mitochondrial O_2 consumption, which promotes the activation of FAO. As mitochondrial uncoupling causes the rise in O_2 consumption, the ATP production will not be increased. This reduces the cardiac efficiency of the cell in the generation and usage of energy, which subsequently reduces the provision of ATP for the cell and leads to contractile dysfunction. Thus, this is the link between the type 2 diabetes mechanism merging with contractile dysfunction and development of muscle pathology, with diastolic dysfunction and left ventricular hypertrophy.

3.5. Genetic mitochondrial heart disease

Genetic MD can be caused by a mutation in either the mtDNA or the nDNA [130, 131]. MDs arising from mtDNA are more prevalent in adults, whereas diseases arising from nDNA tend to be more prevalent in infants and children [132]. MDs can also be classified by the function of the proteins involved in the disease. For example, MDs have been found to be associated with the mutations in genes that encode subunits of the ETC complexes [130] and ATP synthase [133, 134], ancillary proteins that participate in the assembly, transport, and function of the ETC complexes, or the regulatory proteins that control activities of the mitochondria [130, 131]. In addition, mutations have been described in gene-encoding proteins that synthesize cardiolipin, an integral part of the inner mitochondrial membrane [135, 136]. The most frequently identified biochemical abnormalities are deficiencies in NADH-coenzyme Q (CoQ) reductase (complex I) and cytochrome-c oxidase (complex IV) [135, 136].

The mitochondrion is a unique organelle as it possesses its own DNA system. While mutated DNA can affect any organ, the presence of the mtDNA mutations in highly metabolic tissues, such as brain, heart, skeletal muscle, and eyes, exhibits a more severe and progressive prognosis. Patients with the known mitochondrial mutation of m.3243A > G develop early death, whereas if this mutation has a cardiac cause, sudden deaths would occur [137]. A healthy individual may possess mutated DNA, but the onset of the disease will not be obvious until a certain mutation threshold of ~60–90% is present [138]. Inheritance of mtDNA occurs only through the maternal line with single, large-scale deletions being rare and the point mutations frequently transmitted [139].

Cross-sectional studies have shown that specific mitochondrial mutations have been presented with a certain cardiac phenotype, and cardiac disorders could inherit different mtDNA mutations [140]. For example, there are inherited familial cardiomyopathies (in both children and adult) linked to mutations in the mtDNA [139, 141]. Mutation m.1555A > G mt-rRNA has only been associated with restrictive cardiomyopathy [142]. Conversely, up to 40% of MD patients have HCM [143]; atrioventricular (AV) block is one of the manifestations of Kearns-Sayre syndrome (KSS) that is due to the large-scale deletions in the mtDNA [143]. The symptoms of HCM patients who have sarcomeric protein gene mutations differ from the those of MD patients who developed HCM. Generally, these MD patients who develop HCM have left ventricular dysfunction but no left ventricular outflow tract obstruction [144, 145]. Another cardiomyopathy-presenting phenotype that is less common in the MD patients is DCM. The echocardiographic findings showed slow progression of disease [146, 147].

Cardiac phenotype association with genetic MD is more common than realized; however, the mechanism of association of some mutations with specific cardiac phenotypes is not clearly understood. Since myocardial cells depend heavily upon mitochondria for its energy requirements, it is no wonder that specific MD involves specific cardiac pathology phenotype.

4. Clinical applications

4.1. Diagnosis of mitochondrial dysfunction in heart disease

Although it has been widely accepted that mitochondria play a key role in cardiac pathological conditions, effectively diagnosing mitochondrial dysfunction in the clinical setting has been challenging. MDs often affect multiple organ systems in the body and clinical presentation varies; however, there are a few "tell-tale" signs and combinations that may enable clinicians to better identify MDs [148]. For example, patients with KSS, which is typically associated with single deletion mutations, may present with ptosis, retinal pigmentary abnormalities, ataxia, and cardiac conduction abnormalities [148]. In patients with myoclonic epilepsy with ragged-red fibers (MERRF), myoclonus, cerebellar ataxia, and elevated blood lactate are key symptoms in their presentations [149]. A high suspicion is important when considering a diagnosis of MD. Cardiologists who evaluate patients for hypertrophy, conduction abnormalities, and DCM should be aware of the spectrum of MD so that they can collaborate with MD specialists to make accurate diagnoses.

Since there are variabilities in the MD symptom presentations, in addition to the clinical diagnosis, a multiple-parametric approach that involves histological, biochemical, and genetic testing is required to identify abnormalities of blood, urine, or cerebrospinal fluid (CSF) analyte values, microscopic irregularities, biochemical deviations on polarographic assays, or a diagnostic genetic finding [150].

4.1.1. Genetic tests

It is crucial to understand that not all persons with mtDNA mutations will manifest the symptoms. Nuclear DNA and mtDNA mutation screening can be performed in the consented family, but the challenge remains that only a small proportion of these nDNA mutations have been identified. The presence of family history of maternal inheritance or multisystemic diseases will be important to note. Furthermore, mitochondrial genome screening can also be performed on the muscle sample [132].

4.1.2. Laboratory tests

Muscle biopsy in conjunction with molecular genetic testing is required for effective diagnosis of MD [151]. A major feature of the histological result of the biopsy using the Gomori Trichrome stain shows >2% ragged red fibers that come from the sub-sarcolemmal mitochondrial accumulation. However, these ragged red fibers are present only in the late stage of the disease and commonly absent in children [132]. The key diagnostic feature is the presence of fibers that are deficient for cytochrome c oxidase (COX) activity [with >2% of COX negative fibers], reflecting low activity of complex IV of the respiratory chain, in patients less than 50 years [148, 151]. COX activity may be decreased in healthy older patients, so its use in diagnosis is limited to

younger patients. Laboratory tests for the levels of creatine phosphokinase, pyruvate, albumin, lactate, transaminases, and blood count are also recommended [152]. An elevated postprandial lactate:pyruvate ratio (>20) is commonly found in MD patients; however, some MD patients may show normal ratio and thus other tests are required to confirm the disease [146]. Next-generation sequencing is also proposed for screening of the multiple mutations associated with MDs [152]. Additionally, fibroblast growth factor-21 (FGF-21) has been recently identified as a serum biomarker of MDs associated with both mtDNA and nDNA mutations [148], potentially simplifying the clinical diagnosis of MD.

4.1.3. Cardiac imaging

The cardiac presentation of MD patients varies; however, progressive cardiac conduction defects may develop into a complete heart block in KSS, while Wolff-Parkinson-White (WPW) syndrome can develop in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome owing to the m.3243A > G mutation [153, 154]. There is no characteristic manifestation of cardiomyopathy that differentiates MD, although HCM is common [150]. Cardiac imaging using cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) can be used to effectively evaluate the heterogeneous presentation of HCM, offering a more reliable measurement of all segments of the heart than echocardiography [155].

4.1.4. Electrocardiogram

In the early stage of the diagnosis process of MD, 12-lead electrocardiogram results are useful to add to the diagnostic criteria [146]. ECG results will be variable depending on the kinds of syndrome the mitochondrial myopathy is associated with [156]. Ocular myopathy patients may in general show normal ECG profile, but two out of the six patients were presented with ST depression and inverted T wave [156]. Patients with MELAS/MERRF may show atrial or ventricular premature contraction (APC or VPC) with T-wave abnormalities such as inverted T wave, as well as ST depression [156]. These abnormalities can be present even without the presentation of left ventricular hypertrophy [146]. A profile of short PR, or WPW, was also found for a MELAS patient [146, 156]. Patients with KSS presented cardiac conduction abnormalities with a variation of ECG profile of AV blocks, complete right bundle branch block with inverted T, or left axis deviation (LAD) and prolonged His ventricular (HV) interval [156]. Though some patients may show normal ECG profile at diagnosis, performing another ECG every 1–3 years may be important to detect uprise of cardiac abnormalities or complications [151].

4.2. Mitochondria as a drug target in heart disease

Most standard-of-care pharmacological approaches to HF, such as β-blockers, ivabradine, a cyclic nucleotide-gated channel blocker, and antagonism of the renin-angiotensin-aldosterone system, focus on the reduction of the energy requirements of cardiac muscle, including modulation of neurohormonal abnormalities, unloading the heart (vasodilatation), and/or reducing the heart rate, which subsequently reduces myocardial oxygen consumption. Although these therapies have improved survival in patients over the past 2–3 decades, death and poor quality of life continue to adversely affect this ever-increasing patient population [94]. The search for more effective and complementary therapy for these patients must be focused on improving

the intrinsic function of the cardiomyocytes [157, 158], such as finding ways to increase/restore the energy supply, in addition to reducing the energy demand of the heart [1].

Since disruption of metabolic signaling pathways such as in FAO, glucose utilization, or ATP generation contributes to the development of heart dysfunction, proteins in these metabolic pathways have become attractive targets of novel therapeutic strategies for the prevention or early treatment of HF [159]. Selective agonists for each of the PPARs have been established and are currently used to treat hyperlipidemia (fibrates) and diabetes (thiazolidinediones). It must be noted that stimulation of the PPAR pathway in the heart or extra cardiac tissues, e.g., adipose or hepatic tissue, potentially diminishes cardiac lipotoxicity by reducing lipid delivery or increasing mitochondrial oxidation. However, chronic activation of PPARα could lead to deleterious effects, particularly in the context of diabetes, hyperlipidemic states, or the ischemic heart [159].

Additionally, although the molecular mechanisms responsible for mitochondria-mediated disease processes are not yet clear, oxidative stress seems to play an important role. Accordingly, strategies for the targeted delivery of antioxidants to mitochondria are being developed. A typical "mitochondrial cocktail," which may include coenzyme Q10 (CoQ10), creatine, L-carnitine, thiamine, riboflavin, folate, as well as other antioxidants such as vitamins C and E, has been reported to partially improve clinical manifestations, though others have disputed its effectiveness [160]. Although, L-carnitine supplementation may be highly effective in patients diagnosed with DCM secondary to primary systemic carnitine deficiency, supplementation has little effect on other types of mitochondrial cardiomyopathy [132]. Recent developments in mitochondrial-targeted antioxidants that concentrate on the matrix-facing surface of the IMM protect against mitochondrial oxidative damage and hold therapeutic potential for future treatment of cardiovascular diseases (CVDs) [161].

Because a cure for mitochondrial genetic defects is still not available, the management of genetic MD with presentation of cardiac pathology, β-blockers, ACE inhibitors, or angiotensin receptor blockers should be administered [146]. Providing rudimentary nutritional education along with nutritional assessment and exercise will be important for the patients to take preventative measures from further lifestyle disease complications [146, 162]. Should there be advanced second- and third-degree AV block coupled with neuromuscular disorders, a permanent pacemaker is highly recommended [163]. Depending on the severity of the mitochondrial cardiomyopathy, cardiac transplantation could be recommended depending on the presence of neuromuscular weakness as it can complicate anesthesia administration [164].

5. Future direction

Because diagnosing MD can be challenging for clinicians, research is needed to better understand the complex bioenergetic arrangements and redox networks of the mitochondrion in cardiac cell. Improved understanding of mitochondrial mechanism in the pathophysiology in the heart will help the discovery of novel biomarkers and clinical diagnostic standards for the heart disease. In addition, current pharmacologic strategies are incompletely effective, and large randomized controlled trials are warranted to direct future therapy. Since HF is recognized as a state of myocyte energy starvation, greater evidence, in the form of large randomized, controlled trials, is required to confirm the role of metabolic-modulating drugs in the treatment of HF, which

will be expected to be an area of great advances in the future. Additionally, more preclinical and clinical studies are necessary to evaluate the effectiveness and toxicity of mitochondrial-targeted antioxidants. Furthermore, the identification of the mechanisms by which alterations in substrate utilization cause cardiomyopathy is also a necessary area of intense research.

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